Remarks

Applicants have carefully considered this Application in connection with the Examiner's Action and respectfully request reconsideration of this Application in view of the following remarks.

Claims 1 – 6 have been cancelled, and Claims 7 and 8 have been amended to limit them to a method of treating urinary incontinence using a compound of formula II (i.e., the compound DNK333) in free form or in the form of a pharmaceutically acceptable salt. The subject matter canceled from the claims is canceled without prejudice, with the proviso that Applicants may pursue such subject matter at a later time, such as in a continuation application.

Support for the amendments is found, in part, in the first full paragraph on page 7 of the Specification and in the claims as originally filed.

I. Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-8 under 35 U.S.C. §103(a) as being unpatentable over U.S. 2004/0058914 ("Doi"). For the reasons discussed below, Applicants respectfully traverse this rejection.

Applicants have discovered that a compound of formula II (i.e., the compound DNK333) in free form or in the form of a pharmaceutically acceptable salt can be used to treat urinary incontinence. Applicants claim methods of treating urinary incontinence by administering such compound in free form or in the form of a pharmaceutically acceptable salt.

In making the rejection under 35 U.S.C. §103(a), the Examiner states in the Office Action that Doi teaches the administration of the neurokinin receptor antagonist DNK333 (the compound of formula II in Claim 7 in the present application) in the treatment of urinary frequency and urinary incontinence. (See Office Action, p. 2.) The Examiner also states that Doi teaches at paragraph [0393] the administration of an NK_1-NK_2 dual antagonist, such as DNK333, alone, or in combination with an anti-cholinergic. (See Office Action, p. 2.) According to the Examiner, methods of treating

urinary incontinence comprising administering DNK333 is clearly contemplated by Doi, "as evidenced by the multiple recitations thereto throughout the disclosure as well as in the claims", and the Examiner cites paragraph [0506] is support of that statement. (See Office Action, paragraph bridging pages 2 and 3.)

As pointed out in Applicants' previous response, paragraph [0506] in Doi, which is part of the sentence that begins in paragraph [0505] of Doi, is an unsubstantiated claim of efficacy with respect to all of the 14 specifically cited diseases and conditions identified in paragraph [0506], namely urinary frequency, urinary incontinence, asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis, pain, cough, irritable bowel syndrome, emesis, depression, anxiety, manic depression psychosis and schizophrenia. There is no experimental evidence in Doi to support this claim. With respect to all of the cited diseases and conditions except purportedly for urinary incontinence, there is no experimental evidence whatsoever in Doi. With respect to urinary incontinence, as set forth in the previously submitted Declaration of Eckhard Weber under 37 C.F.R. § 1.132 (the "First Declaration"), Doi does not demonstrate that any of the compounds disclosed in Doi are effective to treat urinary incontinence. (See the First Declaration, paragraph 4.)

The only experimental data in Doi that purports to demonstrate the effectiveness of the disclosed compounds in treating urinary incontinence are in Experimental Examples 1 and 2. (See the First Declaration, paragraph 4.) However, that experimental data instead demonstrates the effectiveness of a combination of disclosed compounds in increasing cyclophosphamide-impaired bladder capacity. (See the First Declaration, paragraph 4.) As set forth in the First Declaration, the model used in Experimental Examples 1 and 2 that purportedly tested for the efficacy of a composition with respect to urinary incontinence was based on the treatment of animals under a urethane anesthesia with cyclophosphamide. Instead of testing for the efficacy of a composition with respect to urinary incontinence, the model tested for the efficacy of a composition with respect to increasing bladder capacity. (See the First Declaration, paragraph 4.) As also set forth in the First Declaration, the model used in Doi is a model for cystitis, which is an inflammatory condition. (See the First Declaration, paragraphs 5 and 6.) If inflammation plays a role in urinary incontinence, it is a minor

role. (See the First Declaration, paragraph 6.) As a result, the model used in the Doi reference is a model that is not directed towards a neuromuscular mechanism for urinary incontinence and is not a model for urinary incontinence. (See the First Declaration, paragraph 6.)

As pointed out in the First Declaration, the Experimental Examples in Doi demonstrate that an NK_1 receptor antagonist alone is not effective in treating the condition present in the model employed (see the First Declaration, paragraph 7) and only teach combination therapy as being effective to treat that condition (see the First Declaration, paragraph 10). One of the articles referred to in the First Declaration is Green, et al., "Efficacy and Safety of a Neurokinin-1 Receptor Antagonist in Postmenopausal Women with Overactive Bladder with Urge Urinary Incontinence," The Journal of Urology, Vol. 176, pp. 2535-2540 (2006). A copy of that article was attached to the First Declaration. In the Green article, the results from a clinical trial where an NK_1 receptor antagonist alone was used to treat urinary urge incontinence are presented. The Green article states that the clinical trial demonstrated the efficacy for an NK_1 receptor antagonist in urge urinary incontinence (see page 2538).

The Examiner states that the Green article describes the administration of the NK_1 receptor antagonist, aprepitant, which is not an NK_1-NK_2 dual antagonist and which is not structurally related to DNK333. As a result, the Examiner concludes that "the comparison is misplaced and without merit." (See Office Action, page 3.)

The Applicants would like to respectfully point out that the Green article was cited as evidence that the model used in the Experimental Examples in Doi is not a model for urinary incontinence. If it were a model for urinary incontinence, then it should not have produced data inconsistent with the clinical data of the Green article (i.e., it should not have generated data showing that NK_1 receptor antagonists alone are not effective in treating urinary incontinence whereas the Green article demonstrates that NK_1 receptor antagonists can be effective alone in treating urinary incontinence). (See the Declaration of Eckhard Weber under 37 C.F.R. §1.132 submitted with this response (hereinafter referred to as "the Second Declaration), paragraph 9.) Even though the

compound in the Green article is not structurally similar to DNK333 and is apparently not an NK_1-NK_2 dual antagonist, the Green article is relevant because it provides experimental evidence that the model used in the experimental examples of Doi that purport to show efficacy for urinary incontinence is not in fact a model for urinary incontinence and that Doi therefore provides no experimental evidence that any of its compounds are effective in the treatment of urinary incontinence. (See the Second Declaration, paragraph 9.)

The fact that the model used in Doi is not a model for urinary incontinence would be readily apparent to one of ordinary skill in the art and would be taken into consideration when determining whether or not a compound could be useful for treating urinary incontinence. (See the Second Declaration, paragraph 6.) In other words, when considering the lack in Doi of a model for urinary incontinence and the lack of any experimental evidence in Doi that any of the Doi compounds are useful for urinary incontinence, one of ordinary skill in the art would not conclude that all of the compounds of Doi were useful for treating urinary incontinence, much less that DNK333 was useful for treating urinary incontinence. (See the Second Declaration, paragraph 6.)

As set forth in the First Declaration, the model used in Doi is a model for cystitis, which is an inflammatory condition, and is not a model for urinary incontinence (see the First Declaration, paragraphs 5 and 6), whereas the models used by the Applicants are models for non-inflammatory overactive bladder/urinary incontinence, and the experimental results in the Specification demonstrate preclinical efficacy of the compounds of formula I in the Specification, including DNK333, for the treatment of urinary incontinence (see the First Declaration, paragraph 9). This is in stark contrast to Doi which does not provide any experimental evidence demonstrating that any of the compounds disclosed in Doi are effective to treat urinary incontinence. (See the First Declaration, paragraphs 4 and 10.)

In paragraphs [0505] and [0506], Doi claims that the combined use of an NK_1 receptor antagonist and an anti-cholinergic drug or NK_2 receptor antagonist is effective in treating 14 diseases and conditions, namely urinary frequency, urinary incontinence,

asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis, pain, cough, irritable bowel syndrome, emesis, depression, anxiety, manic depression psychosis and schizophrenia.

Doi focuses on combination therapy of NK_1 receptor antagonists and in particular on the administration of (i) an NK_1 antagonist and (ii) an NK_2 antagonist and/or an anti-cholinergic drug. (See the Abstract of Doi. See also Examples 1 – 4 on page 28 of Doi where the administration of at least two compounds is taught and Experimental Examples 1 and 2 on pages 28 and 29 where two compounds are administered.) (See also the Second Declaration, paragraph 11.) Doi states that compound (T) is an NK_1 receptor antagonist and is "particularly preferable." (See paragraph [0063] in Doi.) In paragraphs [0275] through [0384], Doi identifies 110 preferred compounds, none of which is DNK333. (See the Second Declaration, paragraph 11.) Doi essentially mentions in passing that an NK_1-NK_2 dual antagonist can be administered alone, but does not provide any experimental examples of the administration of an NK_1-NK_2 dual antagonist alone. (See the Second Declaration, paragraph 11.)

In view of the focus of Doi on combination therapy, Applicants respectfully submit that Doi teaches away from Applicants' claimed inventions and would lead one of ordinary skill in the art down an entirely different path when investigating a method of treating urinary incontinence. (See the Second Declaration, paragraph 20.) Doi fails to provide any motivation for one of ordinary skill in the art to specifically select DNK333 from all the various compounds disclosed in Doi and fails to provide any reasonable expectation of success for treating urinary incontinence if DNK333 were selected, especially since the sole experimental model utilized in Doi is not a model for urinary incontinence and all of the examples in Doi are directed to combination therapy. (See the Second Declaration, paragraph 20.) Moreover, as stated in the Second Declaration, Doi does not recognize that urinary incontinence involves a neuromuscular mechanism. (See the Second Declaration, paragraph 6.) Thus, one of ordinary skill in the art would not arrive at Applicants' claimed inventions when the scope of Doi is so divergent from the methods claimed by Applicants.

Applicants respectfully submit that other secondary considerations weigh in favor of non-obviousness. Specifically, additional facts and arguments in support of non-

obviousness of Applicants' claimed inventions are presented herewith in the Second Declaration, which is submitted with this response. The additional data included in Exhibit A to the Second Declaration show unexpected properties attributed to Applicants' claimed inventions. (See the Second Declaration, paragraph 12.) These data show that the compound of formula II (i.e., DNK333) exhibits unexpected properties compared to the multitude of compounds known in the art for the treatment of urinary incontinence. (See the Second Declaration, paragraph 12.) Firstly, DNK333 does not only act on NK_1 and NK_2 receptors, but is a triple antagonist acting on NK_1, NK_2 and NK_3 receptors. (See Examples 1 and 2 of Exhibit A to the Second Declaration and the Second Declaration, paragraph 12.) Secondly, as demonstrated by clinical studies, DNK333 administration is associated with unusually few side effects, i.e., shows excellent clinical safety and tolerability. (See Example 3 of Exhibit A to the Second Declaration and the Second Declaration, paragraph 12.)

Regarding Exhibit A to the Second Declaration, Example 1 shows that DNK333 binds to all three human recombinant neurokinin receptors, namely NK_1, NK_2 and NK_3. (See the Second Declaration, paragraph 13.) Example 2 describes results from functional assays using DNK333 with and without competitive agonists of human native NK_1, NK_2 and NK_3 receptors. (See the Second Declaration, paragraph 13.) As can be seen in Figure 1, increasing amounts of DNK333 were able to competitively block all three receptor subtypes in a concentration-dependent fashion. This further corroborates the findings shown in Example 1 that DNK333 binds all three receptor subtypes (i.e., is a triple antagonist) and is able to effectively compete with the respective receptor agonist. (See the Second Declaration, paragraph 13.) Example 3 describes a clinical study performed with DNK333 and summarizes its results in Table 2. These data show that DNK333 is characterized by a surprisingly high clinical safety and tolerability in patients. (See the Second Declaration, paragraph 14.)

Importantly, these data indicate that DNK333 is not only a compound that can be used in the laboratory, but rather can be used as a medicament in a clinical setting to treat patients suffering from urinary incontinence. (See the Second Declaration, paragraph 15.)

In order to appreciate the significance of these results, it needs to be understood that urinary incontinence is based on a unique pathophysiological role of several neurokinin receptors. (See the Second Declaration, paragraph 16.) One of ordinary skill in the art would readily appreciate the various neurokinin-receptor subtypes and appreciate their role in urinary incontinence. (See the Second Declaration, paragraph 16.) For example, all three neurokinin receptors, NK_1, NK_2 and NK_3, are expressed on cells modulating urinary bladder motor and sensory function. They are solely involved in exaggerated conditions such as those found in urinary incontinence. (See the Second Declaration, paragraph 16.) In other words, it has been found that DNK333 can block multiple neurokinin receptors that are involved in urinary incontinence. (See the Second Declaration, paragraph 16.)

Thus, one of ordinary skill in the art would expect that DNK333 as a triple antagonist would provide for an improved treatment of urinary incontinence compared to a monofunctional NK_1 or NK_2 antagonist, or even a dual antagonist, specifically because urinary incontinence is a disease that involves all three receptors NK_1, NK_2 and NK_3. (See the Second Declaration, paragraph 17.) Moreover, low toxicity and high tolerability of DNK333 further account for an advantageous use. (See the Second Declaration, paragraph 17.)

The blockade of multiple neurokinin receptors with a single compound to treat urinary incontinence constitutes an innovative approach to interfere with pathophysiological mechanisms of urinary incontinence in a polymodal fashion without impairment of normal functions. (See the Second Declaration, paragraph 18.) This unexpected property is lacking in Doi; in Doi there is no indication that DNK333 would bind to all three receptor subtypes or that DNK333 would have any other advantageous properties compared to the other compounds disclosed therein. (See the Second Declaration, paragraph 19.)

According to the Examiner, motivation is provided based on the teachings and suggestions of Doi to administer DNK333 to treat urinary incontinence. (See Office Action, page 3.) Doi, however, fails to provide any motivation for one of ordinary skill in the art to specifically select DNK333 from all the various compounds disclosed. (See the Second Declaration, paragraph 20.) Thus, one of ordinary skill in the art would not have

arrived at an improved method of treating urinary incontinence using DNK333 which has superior properties without exerting inventiveness. (See the Second Declaration, paragraph 20.) In view of the focus of Doi on combination therapy, Doi teaches away from Applicants' inventions and would lead one of ordinary skill in the art down an entirely different path when investigating a method of treating urinary incontinence. (See the Second Declaration, paragraph 20.)

In view of the lack of experimental evidence that any of the compounds of Doi are useful in the treatment of urinary incontinence, the unsubstantiated claim in paragraphs [0505] and [0506] of Doi that the combined use of an NK_1 receptor antagonist and an anti-cholinergic drug or NK_2 receptor antagonist is effective in treating 14 diseases and conditions ranging form cough to urinary incontinence to schizophrenia, the numerous compounds disclosed in Doi, the focus on combination therapy in Doi, the lack of any experiments in Doi where a single compound as opposed to a combination of compounds is used, the lack of recognition in Doi of the unexpected properties of DNK333 as a triple neurokinin receptor antagonist and its low toxicity and high tolerability in humans, one of ordinary skill in the art, despite the disclosure in Doi of DNK333 and the statement in Doi that NK_1-NK_2 dual antagonists may be used alone, would not be motivated to select DNK333 from the numerous compounds disclosed in Doi for the treatment of urinary incontinence nor have any reasonable expectation that a single compound selected from the numerous compounds disclosed in Doi would be successful in treating urinary incontinence. (See the Second Declaration, paragraph 21.) There would be no reasonable expectation of success with respect to a particular compound disclosed in Doi being able to treat urinary incontinence, much less any reasonable expectation that if DNK333 were selected, it would be effective in treating urinary incontinence. (See the Second Declaration, paragraph 21.)

Applicants' discovery that DNK333 can be used to treat urinary incontinence was therefore novel, non-obvious and unexpected at the time of Applicants' claimed inventions, and Applicants' claimed inventions are patentable over Doi.

II. Conclusion

In view of the foregoing, Claims 7 and 8 are in condition for allowance, and Applicants earnestly solicit a Notice of Allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this Application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration to this Reply is respectfully requested.

Respectfully submitted,
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